IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NATERA, INC., *Plaintiff / Counterclaim-Defendant*, v. ARCHERDX, INC., ARCHERDX, LLC and INVITAE CORP. *Defendants / Counterclaimants*.	Case No. 20-125 (LPS) CONSOLIDATED **JURY TRIAL DEMANDED** **FILED UNDER SEAL** **HIGHLY CONFIDENTIAL – ATTORNEYS' EYES ONLY**

DEFENDANTS' OPENING BRIEF IN SUPPORT OF MOTION FOR SUMMARY JUDGMENT AND TO EXCLUDE TESTIMONY

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I. SUMMARY OF ARGUMENT

Summary judgment of no infringement and invalidity on all patents-in-suit is warranted. In many instances, Natera's infringement and validity theories contradict the Court's claim constructions (*e.g.*, "at least two primers," "melting temperature," and "target loci"). In another instance, Natera's theory contradicts the claim language on its face (*e.g.*, "the universal primer"). Applying the Court's constructions and the clear claim language leads to the inescapable conclusion that Defendants do not infringe and that the patents-in-suit are invalid.

Another major defect with Natera's patents stems from the fact that while Natera allegedly made its inventions in 2011, it did not even begin drafting the asserted claims until nearly a decade later in response to the release of products by Defendants. Natera's belatedly drafted claims are unsurprisingly not reflected in its old patent applications. Rather, when it became commercially beneficial, Natera cobbled the claims together from disparate portions of its kitchen-sink style disclosures, which neither enable nor describe the claimed inventions as an integrated whole. Summary judgment of invalidity under § 112 is thus warranted.

The Court should also exclude portions of the opinions of Natera experts Spellman, Quackenbush, and Wojczik for clear *Daubert* violations ranging from admittedly having no expertise on the subject matter except that which was told to them by Natera's lawyers (Mr. Wojczik) to providing conclusory opinions with zero analysis (Drs. Spellman and Quackenbush).

II. NATURE AND STAGE OF THE PROCEEDINGS

Following the completion of fact and expert discovery, Defendants now move for summary judgment and exclusion of evidence. *See* D.I. 60 § 17(b); D.I. 242.

III. STATEMENT OF FACTS

Facts pertinent to each requested ground for summary judgment and exclusion are set forth within the individual argument sections below. As background, a brief summary of the patents-in-suit is as follows.

A. Overview of Patents-in-Suit

The five asserted patents all pertain to variations of polymerase chain reaction ("PCR"), a staple laboratory technique for generating numerous copies of a nucleic acid fragment. To the extent the Court is unfamiliar with PCR, Defendants direct the Court to the following short video: https://www.youtube.com/watch?v=nHi-3jP6Mvc.

The asserted patents all involve "multiplex PCR," in which more than one DNA target locus is amplified at the same time in the same reaction. Attempts at such multiplex PCR reactions are often stymied by the formation of unwanted side products, most commonly referred to as "primer dimers," which result from interactions between primers associated with different DNA loci. The asserted patents explain, for instance, that the "risk of generating such products increases as the number of primers increases. These non-target amplicons significantly limit the use of the amplified products for further analysis and/or assays." D.I. 78-1, Ex. 5 at 3:6-9.

The figure below illustrates this phenomenon. Part A shows two primers associated with different loci binding to each other, rather than their intended targets. When this happens, polymerase may incorporate nucleotides in the directions indicated by blue arrows to generate an unwanted "primer dimer" side product, illustrated in Part B:

Part A Part B

Throughout this suit, Natera has reiterated that its patents pertain to techniques for avoiding primer dimers in multiplex PCR:

> The patent specification explains that sequencing was problematic after multiplex PCR because of artifacts such as primer-dimers formed during the amplification process, skilled artisans were therefore using methods such as microarrays instead of sequencing, and now ***that the patent teaches a way to minimize the formation of primer-dimer artifacts***, multiplex PCR followed by sequencing could be done more effectively.

D.I. 391 (Third Amended Complaint) ¶ 72[1]; *see also id.* ¶ 68; Ex. A ¶ 258.

In particular, the asserted patents teach the alleged "surprising discovery" that one can identify and eliminate certain primers to avoid primer dimer formation:

> The present invention is based in part on the ***surprising discovery*** that often only a relatively small number of primers in a library of primers are responsible for a substantial amount of the amplified primer dimers that form during multiplex PCR reactions. Methods have been developed to select the most undesirable primers for removal from a library of candidate primers. By reducing the amount of primer dimers to a negligible amount (˜0.1% of the PCR products), these methods allow the resulting primer libraries to simultaneously amplify a large number of target loci in a single multiplex PCR reaction. Because the primers hybridize to the target loci and amplify them rather than hybridizing to other primers and forming amplified primer dimers, the number of different target loci that can be amplified is increased.

D.I. 391-2, Ex. 5 at 46:34-48. The patents emphasize the need for primer selection in multiplex PCR, even characterizing this as "essential." *See id*. at 54:44-50; *see also id.* at 48:4-56:67 ("Exemplary Primer Design Methods").

B. The '814, '172, '482, and '220 Patents

The asserted '814, '172, '482, and '220 patent claims all pertain to the use of multiplex PCR with a so-called "nesting" step. Briefly, nested PCR is a technique in which one uses the product of a first PCR as the starting point for another PCR to try and increase the specificity of

[1] Emphasis supplied throughout unless otherwise indicated.

the reaction. Natera did not invent nested PCR, a point both its experts and named inventors have confirmed:

> Q. You don't – you don't dispute that nested PCR was known in the art prior to the 2011 time frame; correct?
>
> A. I do not – I do not dispute that.

Ex. B at 77:1-7[2]; *see also id.* at 75:23-77:7, 83:7-84:17; Ex. C at 51:4-56:14; Ex. D at 160:17-163:5, 254:6-255:17; Ex. E at 97:11-98:15, 104:21-108:18; Ex. F at 146:5-11; Ex. G 68:2-71:6. Importantly, other than claims 6 and 7 of the '220 patent, the asserted patent claims contain no upper limit on the number of target loci, as confirmed by the inventors. *See, e.g.*, Ex. E at 217:17-218:4; *see also* Ex. G at 136:19-137:12.

C. The '708 Patent

The asserted '708 patent claims pertain to a multiplex PCR technique in which the annealing temperature is in excess of the melting temperature of the primers. According to the patent, the inventors "discovered" that increasing annealing temperature makes a PCR reaction more specific:

> Additionally, it was discovered that the annealing temperature can optionally be higher than the melting temperatures of the primers (in contrast to other methods that use an annealing temperature below the melting temperatures of the primers). A higher annealing temperature improves the specificity of the PCR amplification and reduces or prevents amplification of non-target loci.

D.I. 17-2 at 45:58-65. Yet, the concept of increasing annealing temperature to improve specificity was known in the art, as again confirmed by Natera's expert and inventors. *See* Ex. B at 215:2-216:21; Ex. E at 135:4-12, 140:15-143:6; Ex. H at 119:6-122:7; *see also* D.I. 419-10 ¶ 140; Ex. G at 153:10-154:24.

[2] Objections omitted throughout.

IV. ARGUMENTS IN SUPPORT OF SUMMARY JUDGMENT

A. Defendants Do Not Infringe The '482, '172, And '814 Patents

Every claim of the '482, '172, and '814 patents requires a "first" and "second" PCR step, each of which uses the same "universal primer." For instance, claim 1 of the '172 patent recites "performing a first PCR to simultaneously amplify at least 10 target loci using a universal primer," and then "performing a second, nested PCR to simultaneously amplify the at least 10 target loci using ***the universal primer***." D.I. 17-1, Ex. 2 at claim 1. The definite article "the" establishes that in the claims of the '482, '172, and '814 patents, the universal primer in the second step is the same as the universal primer in the first step. *See Guardant Health, Inc. v. Found. Med., Inc.*, No. CV 17-1616-LPS-CJB, 2020 WL 1329513, at *4 (D. Del. Mar. 23, 2020) ("Because definite articles such as 'the' can be 'anaphoric phrases, referring to the initial antecedent phrase,' the Court (like Judge Burke) reads the claim terms 'grouping the plurality of sequence reads' and 'grouping the sequence reads' as referring to the set of sequence reads discussed in the prior step."). When Natera intended to claim ***different*** universal primers in successive PCR steps, it knew how to do so. *See* D.I. 78-1, Ex. 5 at claim 1 (reciting a "first" and "second" universal primer).

There can be no infringement of the '482, '172, and '814 patents because in the Accused Products the primers in the alleged first and second PCR steps are different. The image below shows both the primer in the first PCR (top row) and the primer in the second PCR (bottom row):

AAT GAT ACG GCG ACC ACC GAG ATC TA

AAT GAT ACG GCG ACC ACC GAG ATC TAC AC

Ex. I at 400-01. The second primer is different from the first because the latter has three additional nucleotides (*i.e.*, "CAC"). There is thus no literal infringement of the '482, 172, and '814 patents, which all require the ***same*** universal primer in successive PCR steps.

Although Natera resorts to the doctrine of equivalents ("DOE"), there can be no infringement under the DOE because the disclosure-dedication rule applies. Under that well-established rule, "the doctrine of equivalents is unavailable for subject matter disclosed in a patent but not included in the claims at issue." *MorphoSys AG v. Janssen Biotech, Inc.*, 358 F. Supp. 3d 354, 362 (D. Del. 2019) (Stark, J.). "The disclosure-dedication doctrine does not require the specification to disclose the allegedly dedicated subject matter in an embodiment that exactly matches the claimed embodiment." *See Eagle Pharms. Inc. v. Slayback Pharma LLC*, 958 F.3d 1171 (Fed. Cir. 2020); *see also CSP Techs., Inc. v. Sud-Chemie AG*, 643 Fed. App'x 953, 958–59 (Fed. Cir. 2016) (disclosure-dedication rule is not "one of form requiring us to identify some language specifically stating that an embodiment is an 'alternative'").

Defendants' expert, Dr. Cooper, presented detailed opinions as to where the asserted patents disclose the use of use of ***different*** universal primers in successive PCR steps such that the disclosure-dedication rule necessarily bars the DOE. *See* Ex. J ¶¶ 76-81. Dr. Cooper's opinion is ***embraced*** by Natera. Indeed, Natera's expert, Dr. Quackenbush, proclaimed that Dr. Cooper "***concedes*** that the specifications of the asserted patents describes use of non-identical universal primers in successive rounds of PCR." Ex. K ¶ 37. At deposition, Dr. Quackenbush confirmed that the patents indeed disclose the use of different universal primers in successive PCR steps. *See* Ex. L at 189:22-193:14. This bars the capture of such matter through the DOE.

To the extent Natera and its expert attempt to rebut the disclosure-dedication rule, they simply pointed out that Natera claimed different universal primers in a later-filed continuation patent. *See* Ex. K ¶ 35. Natera seemingly contends that its later-filed patent retroactively negates application of the disclosure-dedication rule to its earlier-filed '482, '172, and '814 patents. *Id.* But Natera's later-filed patent reinforces that the disclosure-dedication rule applies

to its earlier patents. *See, e.g.*, *CSP Techs., Inc. v. Sud-Chemie AG*, 643 F.App'x at 958 (later-filed continuation "reinforces" that disclosure-dedication rule applies to earlier patent because patentee's decision to claim a feature "in the patent in suit and not to claim it in this continuation patent implies an intent for the two patents to cover different claim scope"); *see also In re Bendamustine Consol. Cases*, No. CV 13-2046-GMS, 2015 WL 1951399, at *3 (D. Del. Apr. 29, 2015) ("The fact that claims covering the disclosed subject matter were ultimately allowed in another patent has no bearing on whether they were disclaimed in the patent in question."); *ViiV Healthcare UK Ltd. v. Lupin Ltd.*, 6 F.Supp.3d 461, 473 (D. Del. 2013) ("It would be improper to recapture scope that is absent in the asserted claim, yet present in unasserted claims, under the doctrine of equivalents."). Because there is no literal infringement, and because the disclosure-dedication rule bars DOE, summary judgment of non-infringement of the '482, '172, and '814 patents is warranted.

B. Defendants Do Not Infringe The '708 Patent

1. Summary Judgment Of Non-Infringement Based On The Court's Construction Of The "At Least 2 Primers" Element

All claims of the '708 patent require that "the annealing temperature for the reaction conditions is greater than a melting temperature of the at least 2 primers." Natera's experts opine that this claim element is satisfied if the annealing temperature is greater than ***some***, but not all, of the melting temperatures for the different primers in the reaction. During claim construction, however, the Court held otherwise based on evidence in the prosecution history:

> As the prosecution history makes clear, when multiple primers are involved, an annealing temperature that is ***greater than*** 'a melting temperature of the at least 2 primers' is one that is higher than each individual melting temperature of each primer.

D.I. 243 at 10-11 (emphasis in original). Thus, infringement is possible only where the "the 'annealing temperature' selected is greater than ***each*** of the melting temperatures of ***each*** primer."

Id. at 11 (emphasis in original).

In the Accused Products, however, the annealing temperature is ***not*** greater than the melting temperature of each primer. For example, in VariantPlex CTL, Natera's expert, Dr. Quackenbush, points to a document that allegedly includes six primers with melting temperatures less than the annealing temperature. *See* Ex. M ¶ 368. But in the cited document, there are an additional 622 primers with a listed melting temperature ***greater*** than the annealing temperature. *See* Ex. N. The overwhelming majority of primers in every product identified by Dr. Quackenbush have a melting temperature greater than the annealing temperature. *See* Ex. M ¶¶ 369-81. Thus, none of the Accused Products infringe the '708 patent because, in accordance with the Court's construction, the annealing temperature is ***not*** greater than ***each*** of the melting temperatures. At most, the annealing temperature is greater than ***some*** of the melting temperatures. Summary judgment of non-infringement is warranted.

2. Summary Judgment of Non-Infringement Based on the Court's Construction Of "Melting Temperature"

The Court construed the term "melting temperature" to mean "the temperature at which one-half (50%) of a DNA duplex of each primer and its perfect complement dissociates and becomes single strand DNA." D.I. 244 at 2. The primers in the Accused Products include at least two segments: a first segment that is complementary to the target sequence and a second segment that is not. In determining melting temperature for the purposes of infringement, however, Natera inexplicably considered only the first portion of the primers and completely neglected the second. Natera and its expert apparently believed that the term "primer" somehow refers only to the portion of the primer that is complementary to the target sequence.

The specification, however, is clear that a "primer" encompasses portions that are non-complementary to the target locus. *See* D.I. 17-2 at 19:17-19 ("In some embodiments, the

primers include a tag that is not target specific, such as a tag that forms an internal loop structure."); *id.* at 94:30-33 ("Primers may contain additional functional sequences, e.g. barcodes, or a full adaptor sequence necessary for sequencing on a high throughput sequencing platform."); *id.* at 8:13-19 ("In various embodiments, the test primers include a 5′ region that is not specific for a target locus (such as a tag or a universal primer binding site) followed by a region that is specific for a target locus, an internal region that is not specific for the target locus and forms a loop structure, and a 3′ region that is specific for the target locus."). There is no basis whatsoever to conclude that the claim term "primer" only refers to a fraction of the "primer" that is complementary to the target, especially because Natera's position to that effect is squarely inconsistent with the usage of "primer" in the specification.

In fact, as both of Natera's experts have confirmed, in the parent to the '708 Patent, Natera specifically claimed "primers" with sequences that are not complementary to the target sequence. *See* Ex. O claim 18 ("The method of claim 1, wherein the at least 50 non-identical primers comprise a 5′ region that is ***not specific*** for a target human locus followed by a region that is specific for a target human locus, an internal region that is ***not specific*** for the target human locus and forms a loop structure, and a 3′ region that is specific for the target human locus."); Ex. B at 43:21-46:9; Ex. L at 66:8-68:10.

It is unsurprising that both the claims and specifications of Natera's patents describe "primers" as having sequences that are not complementary to the target DNA. As Dr. Cooper explained, such non-complementary sequences, while unable to be used for amplifying the target, nonetheless participate in the formation of the unwanted primer side products that Natera's '708 patent ostensibly hopes to avoid through the use of an increased annealing temperature. *See* Ex.

DD at 175:20-178:6. In this light, it would make no sense to exclude them from the melting temperature calculation.

Dr. Quackenbush wrongly relied upon melting temperatures that were computed based on only a fraction of the primers in the Accused Products. Ex. K ¶ 55. Natera totally failed to prove infringement with respect to the full primers used in the Accused Products because it did not even try to do so. As shown by Defendants' expert, Dr. Cooper, for every single partial primer that Dr. Quackenbush erroneously cites for his infringement theory, when the melting temperature is computed based on the ***entirety*** of the primer, it is greater than the annealing temperature and does not satisfy the claims. *See* Ex. J ¶¶ 112-121. Summary judgment of non-infringement is thus warranted.

3. Summary Judgment For Failure Of Proof That The Accused Products Satisfy The Claimed Annealing/Melting Temperature Relationship

As noted above, the claims of the '708 Patent require an "annealing temperature" that is greater than the "melting temperature" of the primers. The "melting temperature" of the primers is a physical property for which it is undisputed different measurement techniques yield radically different results. D.I. 177 at 65-67, 74-75. Therefore, to avoid indefiniteness, the "patent and prosecution history must disclose a single known approach or establish that, where multiple known approaches exist, a person having ordinary skill in the art would know which approach to select. Particularly this is so where different approaches to measurement are involved." *Dow Chem. Co. v. Nova Chems. Corp. (Can.)*, 803 F.3d 620, 630 (Fed. Cir. 2015) (internal citations omitted).

The '708 Patent is indefinite for failing to teach a defined measurement method that gives fair notice of what the claims cover. *See infra* Part IV.E. Natera contends that the '708 patent avoids indefiniteness by teaching the use of the Primer3/SantaLucia software or, alternatively, an ultraviolet light experimental method. *See id.* To the extent Natera is correct, summary

judgment of non-infringement is appropriate because Natera has not shown that the Accused Products have melting temperatures less than the annealing temperatures when those melting temperatures are determined using the methods the '708 patent allegedly teaches.

Neither Natera nor its expert even bothered to compute the melting temperature for even a single primer in Defendants' products. Dr. Quackenbush could have computed melting temperatures, but did not. Ex. L at 33:25-34:13. Instead, Dr. Quackenbush relied only upon melting temperatures in sundry documents Defendants produced. Dr. Quackenbush has no idea how the melting temperatures in these documents were determined:

> Q. For any of the melting temperatures that you rely upon in your report that were provided by Archer, do you know how they were computed?
>
> A. Off the top of my head, I can't tell you directly, no. The important thing, though, is that Archer is reporting primers with -- well, they're reporting annealing temperatures for these primers. And -- well, they're reporting annealing temperatures for these primers. I'll leave it at that. I don't know -- I'm not sure what Archer uses in individual applications, and I don't recall finding that in their documentation.

Id. at 208:9-208:21; *see also id.* at 207:4-15, 207:21-208:1, 227:4-228:25. Because Natera has not shown that the Accused Products have melting temperatures that satisfy the claims when determined using the methods allegedly required by the '708 patent, summary judgment of non-infringement is warranted.

C. Defendants' PCM, Stratafide, and LiquidPlex Products Do Not Infringe Any Of The Asserted Patents

During claim construction, the Court construed the term "target loci" in all of the asserted patents to mean "selected segments of nucleic acid of interest of an individual," explaining that "an individual" means "one and only one individual." D.I. 244 at 1; D.I 243 at 5-6. Under this construction, Defendants' PCM, Stratafide, and LiquidPlex products do not infringe.

According to Natera, Defendants' PCM, Stratafide, and LiquidPlex products infringe through the analysis of circulating tumor DNA, or "ctDNA" for short. *See* Ex. M ¶¶ 99, 103, 107. It is undisputed that in Defendants' products, this ctDNA is mixed in with circulating non-tumor DNA from the cancer patient harboring the tumor. The former is never separated from the latter, and DNA from both sources is input to the assay. Under these circumstances, there can be no infringement because, according to Natera's own experts, this process involves loci from two individuals, not just one.

Natera's infringement expert, Dr. Quackenbush, opines that Natera's Signatera product, which uses ctDNA, practices Natera's U.S. Patent No. 10,526,658. *See* Ex. M ¶ 573. This patent shares the same specification as the asserted '220, '814, and '172 patents, and its claims require a sample that "comprises DNA from the first individual and DNA from the second individual." Ex. P at claim 1. Natera's ctDNA product, Signatera, allegedly practices this claim element because, as Dr. Quackenbush stated, the cancer patent is one individual while the tumor itself is a different individual:

> And so if I were to interpret this, Individual No. 1 would be the cancer patient, and Individual No. 2 would be the tumor whose DNA differs from the DNA of the individual who has that tumor.

Ex. L at 40:6-10. Following this logic, Defendants' ctDNA products do not infringe because they analyze DNA from not just one individual, as the Court's construction of target loci requires, but two individuals.

Notably, Natera's invalidity expert, Dr. Spellman, agreed with Dr. Quackenbush that a tumor is one individual and a cancer patient is a different individual in the context of Natera's patents:

> Q. But you would not say that a tumor is an individual; right?

A. I have seen it characterized that way. Right. Like, we talk about individual tumors. So it's an unusual construction, and it's certainly not the plain language interpretation. But for a – for a specific skill set and scientist, they would understand that that could be a use of this.

Q. Okay. So in Signatera, who would the first individual be?

A. In my construction, the first individual would be the tumor.

Q. And then who would the second individual be?

A. As I've said, the second individual would be the unfortunate person who had a tumor growing.

Ex. B at 51:11-52:17. He understood this as the basis for Dr. Quackenbush's opinion that Signatera practices Natera's '658 patent:

Q. Now, what's your explanation for why Dr. Quackenbush contends Signatera practices the '658 patent when it refers to a first individual and a second individual?

A. I mean, I think the – the model that I gave is the basis for that assertion.

Q. Okay. Now – and that's – and that's that the first individual is a tumor, and that the second individual is the unlucky cancer patient?

A. I believe I have that correct, yes.

Id. at 53:19-54:7.

Therefore, according to Natera's own experts, there can be no infringement by Defendants' PCM, Stratafide, and LiquidPlex products because they involve analysis of DNA from two individuals and the term "target loci" requires the analysis of only one individual.

D. The '708 Patent Is Invalid In View Of Blomquist

Summary judgment of invalidity of the '708 patent is warranted because there is no genuine dispute that the Blomquist reference anticipates or renders obvious all three asserted claims in the '708 Patent. Blomquist discloses multiplex PCR using 178 pairs of primers, all designed with Primer3 software to have a melting temperature of 68°C. Ex. Q at 5. The 45-cycle PCR protocol involves an annealing step of 4 minutes that starts initially at 72°C and decreases by 1°C after every 5 cycles until 64°C is reached. *Id.* at 6. In his report, Dr. Cooper presented detailed

opinions establishing that the asserted '708 patent claims are invalid in view of Blomquist. D.I. 419-10 ¶¶ 255-65. Natera's expert, Dr. Spellman, presented hardly any response. Ex. A ¶¶ 89-91.

As to claim 1, Dr. Spellman half-heartedly alleged in his report that the requirement for the "annealing temperature" element to be greater than the "melting temperature" is not disclosed. *Id.* ¶ 89. This was the only aspect of claim 1 that Dr. Spellman disputed. In Blomquist, however, this relationship is satisfied in the first 20 PCR cycles when the annealing temperature is 72°C, 71°C, 70°C, and 69°C, since the primers all have a 68°C melting temperature. Natera's expert, Dr. Spellman, agreed at deposition:

> Q. When the annealing temperature in Blomquist is 72 degrees down to 68 degrees, that will be higher than the melting temperature of the primers; right?
>
> A. During the portion of the PCR reaction that runs that way, early on, that is correct.

Ex. B at 174:22-175:4.

In his report, Dr. Spellman's specific objection was that "the melting temperature of the primers is ***not*** greater than the ***annealing temperature of the reaction conditions***, when the annealing temperature of the reaction condition is at 68°C or less." Ex. A ¶ 89 (emphasis in original). This sloppy assertion makes no sense. In Blomquist, the primer melting temperature was 68°C, which is greater than the annealing temperature when the annealing temperature is less than 68°C.

To the extent Dr. Spellman instead intended to opine that the annealing temperature is less than the melting temperature when the annealing temperature is less than 68°C, this is simply irrelevant. Nothing in the claims requires that the annealing temperature exceed the melting temperature throughout an ***entire*** PCR protocol. The claims merely require "subjecting the

reaction mixture to primer extension reaction conditions to produce amplified products." This process of "subjecting the reaction mixture" to the "reaction conditions" may, or may not, encompass an entire PCR experiment. Indeed, claim 1 is an open-ended "comprising" claim and as such, encompasses processes with steps where there are "primer extension reaction conditions" that do not use an annealing temperature greater than the melting temperature so long as there are also steps involving "primer extension reaction conditions" where the annealing temperature is greater than the melting temperature.

As to asserted dependent claim 9, which requires that "at least 10 target loci are amplified with at least 10 primers," Natera's expert did not dispute that Blomquist discloses this and otherwise presented no rebuttal to Dr. Cooper's invalidity opinion. *See* Ex. A ¶¶ 89-91.

Finally, as to dependent claim 19, which recites the use of cell-free DNA, Dr. Spellman simply asserted that Blomquist does not disclose this. Yet, Dr. Cooper presented detailed obviousness opinions regarding the use of cell-free DNA. *See* D.I. 419-10 ¶¶ 265, 120-125. Dr. Spellman provided no rebuttal. *See* Ex. A ¶ 91. When asked about this, he simply insisted that cell-free DNA was a "known entity" well before the '708 Patent's priority date:

> Q. Dr. Cooper asserts in paragraph 265 of his report that it would have been obvious to apply Blomquist's cell-free DNA. Do you have any basis for disputing that assertion? And if so, please tell me where it is in your report?
>
> A. I will say again that cell-free DNA was a known entity in 2010 or 2011. I'm not sure what else you want me to say.
>
> Q. What do you mean by it was "a known entity"?
>
> A. There had been a number of papers that have – had come out since circa 2000-ish that had shown in cell-free DNA was present in many bodily fluids, the primary source being cleared plasma, plasma cleared of cells for – for a collection of DNA.

Ex. B at 178:20-179:15. Thus, after failing to rebut Dr. Cooper's obviousness opinions in his report, Dr. Spellman confirmed them at deposition.

Summary judgement is proper here, where there is no genuine dispute that Blomquist anticipates claim 1 of the '708 patent and renders the only disputed dependent claim obvious.

E. The Claims Of The '708 Patent Are Indefinite

The claims of the '708 patent require an "annealing temperature" that is greater than the "melting temperature" of the at least two primers in the PCR reaction. The claims are thus defined in terms of a measurable physical parameter: the primer melting temperatures. It is undisputed that there are numerous different techniques for computing these primer melting temperatures and that these methods lead to radically different results. *See* D.I. 177 at 65-67, 74-75; Ex. B at 21:2-22:5. To provide fair notice to the public about the scope of this private right, the claims are indefinite if "nothing in the record suggests using one method in particular." *Ball Metal Beverage Container Corp. v. Crown Packaging Tech., Inc.*, 838 F. App'x 538, 542 (Fed. Cir. 2020) (internal citations omitted). As demonstrated below, there is no genuine dispute that the claims are indefinite.

1. The '708 Patent Does Not Specify A Particular Melting Temperature Method For Use With The Claims

Far from identifying a particular method for computing melting temperatures, the patent broadly states no less than 25 times that the melting temperature may be any temperature "such as the empirically measured or calculated Tm." *See* D.I. 17-2 at 3:1, 45, 52-53, 59-60, 64-65; 4:1, 9; 64:58, 62-63; 65:43-44, 47-48; 66:32-33, 47-48; 79:64-65; 80:4-5, 14-15, 23-24, 33-34, 37-38, 44-45, 49-50, 56-57, 63-64; 81:8, 16-17. This encompasses every technique known to humankind for determining primer melting temperatures. The patent's repeated reference to the generic "empirically measured" or "calculated Tm" establishes that the patent does not provide fair notice of a particular melting temperature measurement technique to determine infringement and/or invalidity.

Natera attempts to identify particular techniques to save the patent from an invalidity holding: an experimental technique based on UV light and a calculation method using a Primer3 software. Natera's reliance on these two methods worsens the indefiniteness problems with this patent and confirms that summary judgement is warranted.

As to the UV light method, the patent does the exact opposite of suggesting that it is a method appropriate for use with all embodiments of the claims to determine whether a process is covered. Rather, the patent explains vaguely that it can be used with "some embodiments." *See id*. at 81:53-56 ("In ***some embodiments***, the empirically measured Tm (the actual Tm) is determined by using a thermostatted cell in a UV spectrophotometer.").

The situation with the Primer3 calculation method is even more problematic. Again, rather than clearly stating that Primer3 is generally appropriate to use to confirm patent scope, the patent broadly states that it may be used "***in some embodiments***." *Id*. at 61:38-41, 81:42-46; *see also id.* at 47:49-53. What's more, the Primer3 software referred to in the patent includes at least two different techniques for computing melting temperature, one of which was the "default" and one of which was a subsequently developed method that was "recommended," but not actually the default until later versions of the software. *See* Ex. R at 25. It is undisputed that these two techniques yield very different results. *See, e.g.*, D.I. 419-10 ¶ 896.

Natera nonetheless points to Example 25 in the patent and contends that the skilled artisan would understand from this that the non-default "recommended" method, which uses so-called "SantaLucia parameters," is what should be used for the purposes of the patent. *See* Ex. A ¶ 319. The patent, however, confuses this too. Instead of stating that one should use the SantaLucia parameters generally, the patent again open-endedly teaches that these may be used "in some embodiments." D.I. 17-2 at 81:42-46. The text of Example 25, for its part, is merely a cut-and-

paste of a portion of the old Primer3 manual. *Compare* Ex. R at 25 *with* D.I. 17-2 at 235:48-236:45. To the extent the manual referred to the "SantaLucia" parameters as "recommended," and to the extent the inventors cut-and-paste this into their patent, this is far from a clear directive to use those parameters. If it was so clear that the SantaLucia parameters should be used, why was this not even the default in the software?

Unsurprisingly, it is impossible to determine from Example 25 whether the inventors actually used the "default" parameters or went to the trouble of specially instructing the software to use the allegedly "recommended" option in Primer3. As Natera's expert confirmed in deposition, the patent does not disclose the identity of the primers in the example:

> Q. In Experiment 25 there is a reference to a 3,168-plex reaction. Do you see that?
>
> A. Yes, I do.
>
> Q. What primers were used in that 3,618-plex reaction, do you know?
>
> A. I don't think it describes what the primers were here. I don't know if there is a table included in the patent that might have those 3,168 primer pairs, but I don't believe it does.

Ex. C at 203:1-11. A skilled artisan reading the patent thus cannot reverse engineer Experiment 25 to figure out whether the inventors used the "default" parameters in Primer3 or changed the input to use the newly-developed "recommended" parameters or some other variant.

The patent does not teach a particular method (or pair of methods) for computing melting temperature, and the claims are indefinite. In fact, as documented below, Natera has unambiguously informed the public that this is so.

2. Natera Has Informed The Patent Office And Public That Melting Temperatures May Be Computed Using Undisclosed Methods

Natera's experts contend that the skilled artisan would understand from the patent that one should use the Primer3 software with SantaLucia parameters to compute melting temperatures and,

if this does not work, the UV light method. *See, e.g.*, Ex. C at 200:10-202:7; Ex. A ¶ 313. Natera has informed the Patent Office and public, however, that this is not so and that the claims encompass an undefined array of unidentified techniques for computing melting temperatures, including methods not mentioned in the patent. Perhaps more than anything else, this evidence proves that there is no genuine dispute as to indefiniteness.

It is undisputed that Primer3 does not work to compute melting temperatures for primers longer than 35 nucleotides. *See* Ex. B at 225:1-7; Ex. C at 194:3-195:15. Nevertheless, during prosecution, to compute the melting temperature of a primer longer than 35 nucleotides when distinguishing a prior art reference, the patentees did not use the UV light method as its litigation experts now contend they should have. Instead, they employed a ***third*** method that is never even mentioned in the patent—Bolton and McCarthy. *See* Ex. S at Table 1 ("As Primer3 spec Santalucia model is not valid for oligo longer than 35bp. For longer sequence Tm is calculated using the formula from Bolton and McCarthy…."). Natera's claim construction expert, Dr. Quackenbush, had never even heard of this method. *See* Ex. C at 198:11-199:8. Natera's calculations that it submitted to the Patent Office to obtain the patent show that Bolton and McCarthy and Primer3/SantaLucia methods yield significantly different melting temperatures. *See* Ex. S at Table 1 (showing approximately six degrees difference between calculated melting temperatures).

Throughout this case, Natera has failed to convincingly explain away its statements to the public that techniques other than Primer3 and UV light can indeed be used to determine melting temperatures for the purposes of measuring the scope of the claims of the '708 patent. In his report, Natera's expert discounts Natera's reliance on Bolton and McCarthy as coming "from a different Natera patent application." *See* Ex. A ¶ 314. But the Natera patent application where

Natera used Bolton and McCarthy is the direct parent to the '708 patent and has the exact same specification. The claim language at issue then is ***identical*** to the claim language at issue here, except that it refers to "50 non-identical primers" instead of just two. *See* Ex. O at claim 1 ("wherein the annealing temperature for the reaction conditions is greater than a melting temperature of the at least 50 non-identical primers").

Dr. Spellman's only other rejoinder to Natera's reliance on Bolton and McCarthy is to suggest that it is irrelevant because it is absent from the '708 patent. *See* Ex. A ¶ 314. Yet, the absence of Bolton and McCarthy from the patent underlines the confusion it creates for the measurement of the scope of the '708 patent. If it were truly the case that one would understand from the '708 patent that either Primer3 or UV should be used to compute melting temperatures, Natera itself never would have used something different before the Patent Office.

Notably, when confronted with the issue during deposition, Dr. Spellman had no explanation for why Natera used the undisclosed Bolton and McCarthy method instead of the UV method:

> Q. Now, do you have any explanation for why they didn't do a UV-Vis experiment?
>
> A. I have no reason why they didn't do a UV-Vis experiment.
>
> …
>
> Q. Now, my next question is, do you have any explanation for why they relied upon Bolton and McCarthy and submitted it to the patent office, even though it wasn't disclosed in the patent?
>
> A. I'm sorry. I don't actually know what HFEW2 with the 13 base pair tails is for, so it's very difficult for me to speculate why they might be doing this. I could spend some time looking up, trying to understand it, if you'd like.

Ex. B at 232:2-233:9.

3. The Claims Are Still Indefinite Even If The Patent Directs Skilled Artisan To UV Light And Primer3

Even assuming wrongly that the patent guides a skilled artisan to the UV light and Primer3/SantaLucia methods, this would simply further prove indefiniteness because it is undisputed that these methods yield very different results. The scientific literature has compared these very methods. In the figure below, the black line represents the UV light method while the red dots shows Primer3/SantaLucia:

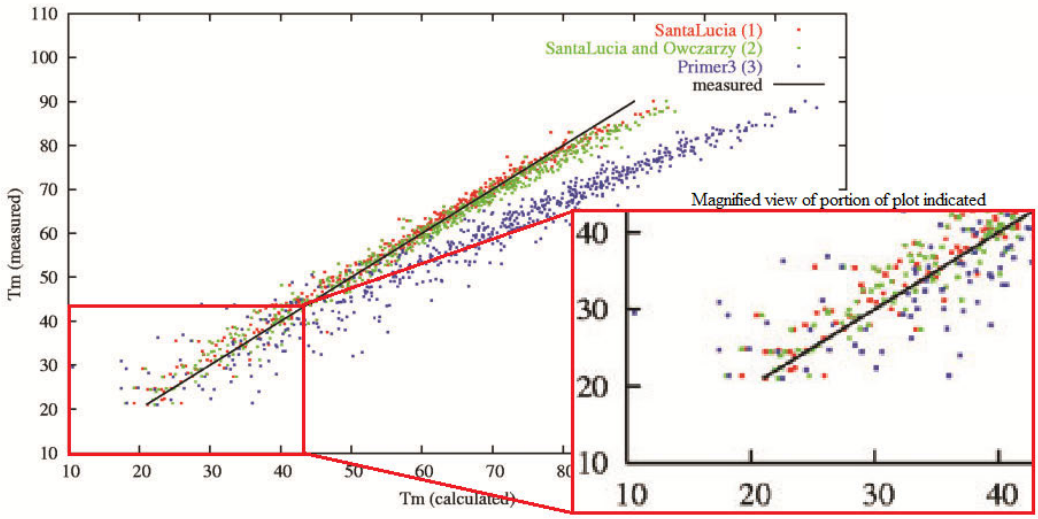

Fig. 1. The correlation between predicted and measured melting temperatures for three different T_m calculation methods. Methods (1) and (2) were implemented into the modified version of Primer3. Method (3) corresponds to the original version of Primer3. For primers of typical length (15 30 nucleotides) the average differences between the experimental and predicted T_m were 1.37, 1.78 and 11.70°C for methods (1), (2) and (3) respectively. The experimental melting temperature data used in this analysis were retrieved from the literature (Owczarzy *et al.*, 2004) and include 590 different measurements with 146 different oligonucleotides.

D.I. 419-10 ¶ 896. It is at once apparent that most of the data points in red are more than one degree away from the black line that represents a perfect match between the two methods. For example, one data point, at the approximate coordinate (25,35), shows an almost ten degree difference between the two methods.

Dr. Spellman nonetheless opines that because the average difference between the UV and Primer3/SantaLucia methods is 1.37°C, the two methods are "tightly correlated" and a skilled artisan would understand that "the different methods do not result in materially different outcomes, *i.e.*, melting temperature measurements are within a couple of degrees Celsius." Ex. A ¶ 311.

The patent, however, teaches that these two techniques do, in fact, yield "materially different outcomes." As Defendant's expert, Dr. Cooper, pointed out, the specification explains that the annealing temperature must exceed the melting temperature by just one degree. *See* D.I. 419-10 ¶ 895; D.I. 17-2 at 79:62-80:30 ("In various embodiments, the annealing temperature is between 1 and 15° C (such as between 1 to 10, 1 to 5, 1 to 3, 3 to 5, 5 to 10, 5 to 8, 8 to 10, 10 to 12, or 12 to 15° C., inclusive) greater than the melting temperature…"); D.I. 17-2 at 3:42-49 ("In various embodiments, (i) the annealing temperature is at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 15° C. greater than the melting temperature…"); *id.* at 6:45-51 ("In some embodiments, the annealing temperature is at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 15° C. greater than the melting temperature…"). Whether the difference between the methods is 1.37°C or "a couple of degrees," the UV light and Primer3/SantaLucia methods yield materially different results. In fact, if the ***average*** deviation between Primer3/SantaLucia and UV light methods is 1.37°C, it simply confirms that for individual primers the Primer3/SantaLucia melting temperature is frequently far different than the UV light melting temperature.

Thus, even if one accepts virtually every aspect of Natera's theory, the claims of the '708 patent are still undisputedly indefinite.

4. The '708 Patent Is Indefinite For Failing To Specify Conditions For Determining Melting Temperature

Whether it is the UV light, Primer3/SantaLucia, or another method, the '708 patent claims are further indefinite for not specifying the conditions that should be used for determining primer melting temperature. As the parties and their experts agree, the conditions in which the primer exists affects melting temperature. *See* D.I. 177 at 75; Ex. C at 188:8-193:3 ("But even with Primer3, if I were to change the conditions, it would give me different estimates of temperatures because my reaction conditions were different.").

Natera's expert assumes without basis that one should use the PCR "reaction conditions" for determining primer melting temperatures. *See* Ex. A ¶ 317. Yet, there is nothing in the claims that warrants this assumption. While the claim expressly ties the PCR "reaction conditions" to the claim terms "primer extension," "annealing temperature," and "annealing step," it does not tie the "reaction conditions" to the "melting temperature." *See* D.I. 17-2 at claim 1. For instance, claim 1 recites "wherein the annealing temperature for the reaction conditions is greater than ***a melting temperature*** of the at least 2 primers." Referring broadly to "a melting temperature," nothing in this language justifies the assumption that the PCR "reaction conditions" should be used for determining melting temperature.

In fact, the specification expressly teaches that one cannot simply assume that the PCR "reaction conditions" should be used for determining primer melting temperatures. According to the specification, this is just one of multiple choices:

> ***In some embodiments, one or more of the following conditions are used*** for empirical measurement of Tm or are assumed for calculation of Tm: temperature: of 60.0° C., primer concentration of 100 nM, and/or salt concentration of 100 mM. ***In some embodiments, other conditions are used***, such as the conditions that will be used for multiplex PCR with the library. In some embodiments, 100 mM KCl, 50 mM $(NH_4)_2SO_4$, 3 mM $MgCl_2$, 7.5 nM of each primer, and 50 mM TMAC, at pH 8.1 is used.

Id. at 81:34-42. Thus, neither the claims nor the specification directs the skilled artisan to a particular set of conditions for determining melting temperatures, rendering the claims indefinite.

F. The Asserted Patents Are Not Enabled To Their Full Scope

Natera's patents encompass subject matter far beyond what the specification supports. There is no genuine dispute that Natera's claims are thus invalid for lack of enablement.

Directly relevant here is *Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371, 1378–79 (Fed. Cir. 2007). In that case, the Federal Circuit considered claims directed to fluid injectors, construing them to encompass embodiments both with and without a "pressure jacket." The

evidence, however, established that skilled artisans could not make and use embodiments ***without*** the pressure jacket absent undue experimentation. The Federal Circuit thus invalidated the claims for lack of enablement, even though the specification may have enabled embodiments ***with*** the pressure jacket. *Id.* at 1379-80. "The irony of this situation," the Federal Circuit explained, was that the plaintiff "successfully pressed to have its claims include a jacketless system, but, having won that battle, it then had to show that such a claim was fully enabled, a challenge it could not meet. The motto, 'beware of what one asks for,' might be applicable here." *Id.* at 1381.

This motto is equally applicable in this case. Natera drafted overbroad claims and secured a correspondingly broad claim interpretation. Natera cannot now meet the challenge of showing that its claims are fully enabled.

1. Background Of The Enablement Issue

All asserted claims in this case are directed to the performance of PCR on multiple nucleic acid targets in the same reaction volume at the same time, a process referred to as "multiplex PCR." With the exception of two dependent claims in Natera's '220 patent, the claims are unlimited in the number of targets in the multiplex PCR.[3] As Natera and its experts have made clear, however, as the number of targets increase, multiplex PCR quickly becomes unworkable because of unintended cross-reactions between primers from different targets that create unwanted side products, such as "primer dimers." *See, e.g.*, D.I. 391 ¶¶ 70, 72; Ex. A ¶¶ 202, 229-230; Ex. M ¶¶ 52-53. Natera's inventors testified extensively to this effect. *See, e.g.*, Ex. E at 34:16-37:19, 76:15-77:8, 114:18-115:8, 116:6-117:25; Ex. H at 97:3-98:25, 115:21-117:14,145:15-146:4; Ex.

[3] The two claims in the '220 patent have an upper limit of 5,000 targets. As to the other claims, Natera has suggested that there is some upper limit of "more than a million" primers. Ex. A ¶ 264. While such an assertion is without basis, whether the upper limit is 5,000 or 1,000,000, the claims are still not enabled.

G at 65:14-66:21; Ex. F at 100:14-101:1, 121:20-122:5, 129:3-9, 164:16-166:12.

Based on the overwhelming evidence in the specification regarding the role of primer selection in avoiding primer side products, Defendants argued during claim construction that the claims should be construed to require "primers with sequences complementary to the nucleic acid ***selected to avoid primer side products***." *See, e.g.*, D.I. 177 at 13-17. Natera opposed this, arguing that the claimed inventions "avoid the use of primer dimer side products, but it's not through selection of the target loci and it's not through selection of the primers themselves." D.I. 185 at 34:9-18; *see also id.* at 6:3-10, 6:19-7:2, 12:12-22. Although Natera has never explained how this is allegedly accomplished, the Court adopted Natera's position as a matter of claim construction based on the claim text. D.I. 243 at 6.

Thus, the claims as construed by the Court are both unlimited in the number of target loci and include no constraints whatsoever on the selection of loci or primers to avoid side products. The question now, then, is whether Natera can meet the challenge of showing that the skilled artisan could make and use the invention without utilizing such primer/loci selection techniques to avoid primer dimers. Natera, like the plaintiff in *Liebel-Flarsheim*, cannot do so.

2. The Specification Establishes That The Claims Are Not Enabled

The patents themselves could not be clearer. To avoid unwanted side products and allow successful multiplex PCR, it is "essential" to remove the primers (the particular DNA sequences of the primer) that cause such side products:

> At high multiplexing it is not possible to eliminate all spurious interactions, but it is ***essential*** to remove the primers or pairs of primers with the highest interaction scores in silico as they can dominate an entire reaction, greatly limiting amplification from intended targets.

D.I. 78-1, Ex. 5 at 54:46-50; *see also id.* at 3:4-9; D.I. 419-10 ¶ 770. The Court's construction, however, cemented that the claims include no limitations to this effect. And indeed, the lead

inventor on Natera's patents and its vice president of R&D, Dr. Bernhard Zimmerman, testified that the claims themselves do "not teach any specific ways of excluding primer dimer." Ex. E at 233:19-235:3. As he bluntly stated, "I do not think that the problem of primer dimers is addressed in this claim." *Id.* at 226:3-9; *see also id.* at 235:24-236:8, 237:18-238:7, 248:3-249:1. Thus, the claims are defective on their face.

3. Natera's Witnesses Confirm Lack Of Enablement

Far from suggesting that the claims are not defective, Natera's experts and inventors confirmed that to practice the claimed invention one would need to do the very thing that Natera successfully convinced the Court is not actually in the claims (*i.e.*, use specific primers [made up of specific DNA sequences] to avoid unwanted side products). As in *Liebel-Flarsheim*, this establishes lack of enablement.

Natera's invalidity expert, Dr. Spellman, testified that it is "almost impossible to do PCR without designing primers." Ex. B at 194:9-16. When asked if any of the working examples in the patents do not involve primer selection to avoid primer dimers, Dr. Spellman responded that "[y]ou can't do PCR without designing primers. It is the very first step." *Id.* at 194:21-195:5; *see also id.* at 196:4-197:1. He explained that "as you add more primers into the mix, the number of interaction terms you have to deal with increases. So it is ***essential*** when doing PCR to pick primers." *Id.* at 198:6-199:4; *see also id.* at 199:5-14.

In his report, Dr. Spellman hypothesized that using the disclosure in the patents, a skilled artisan could potentially carry out a multiplex PCR with 280,000 targets.[4] *See* Ex. A ¶ 267. But

[4] He testified that he chose this limit because the largest multiplex PCR in the patents involved 28,000 targets and in his "experience" it is the case that "not always, but often," a technology can be "scaled up in order of magnitude without fundamentally new inventions." Ex. B at 201:20-25. Because it is undisputed that the claims encompass far beyond 280,000 primers, such testimony is yet another admission that the claims are not enabled. In this regard, this case parallels *MagSil Corp. v. Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377 (Fed. Cir. 2012).

tellingly, Dr. Spellman equivocated about higher scale multiplex PCRs—which are undisputedly within the scope of the claims. At deposition, when asked whether a skilled artisan could perform a 560,000-plex PCR without undue experimentation based on the patent disclosure, he testified that it was "plausible," but that he "honestly" did not know. Ex. B at 202:16-203:6. When asked about a million-plex PCR, Dr. Spellman could not even say how probable it was that a skilled artisan could make it work based on the patent disclosures. *Id.* at 203:18-204:21. If the specification truly enabled such large-scale PCRs, Dr. Spellman would have said so.

Even if one leaves open the possibility that PCRs involving a million targets could be carried out in some way based on the patents without undue experimentation, Dr. Spellman's testimony still establishes lack of enablement. This is because he testified that ***unless*** one did the PCRs using the very thing that is not required under the Court's construction (selection of primers to avoid side products), the PCR would not work and would yield "garbage:"

> Q. In your proposed 280,000-plex PCR, if you didn't go through the process of identifying the pairs of primers that are likely to cause primer dimers and eliminating those, what would happen in your PCR?
>
> A. As I said, Counsel, primer design, including all components of primer design, is essential to make PCR work. ***It does not work if you don't design primers.***
>
> * * *
>
> Q. And so what would happen if you didn't go ahead and remove those primers that were likely to cause primer dimers when you set out to do your 280,000-plex PCR?· What would happen? Would it not work?
>
> A. It is very likely that without thoughtful primer design, ***you will get garbage***.

Id. at 206:6-16; 206:22-207:5. Notably, Dr. Spellman's answers were not confined to 280,000-

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There, the Federal Circuit invalidated claims that recited an infinite scope "in the area of resistive change," where the specification established that the inventors had achieved only an 11.8% improvement. *See id.* at 1380-84. In a prior litigation, Natera has made abundantly clear the extent to which *MagSil* is applicable here. *See, e.g.*, Ex. EE at 17-19; Ex. FF ¶ 675; D.I. 419-10 ¶¶ 797-98.

plex PCR, but addressed multiplex PCR generally. He stated that "examining primers for primer dimer formation is an essential component of PCR at all levels." *Id.* at 206:1-3. Following *Liebel-Flarsheim*, this testimony proves non-enablement because, under the Court's construction, one must be able to make and use the inventions not just with primer selection, but also without it.

Natera's infringement expert, Dr. Quackenbush, echoed Dr. Spellman. When asked to identify the techniques used in the "claimed invention" of the '220 patent that avoid primer dimers, he identified the very thing that the Court ruled the claims do not require (*i.e.*, primer selection):

> And again, one skilled in the art would understand that the patent in its specification itself instructs us to use primer 3. Primer 3 is a technology or is a primer design tool that, in fact, was constructed to avoid the formation of primer dimers, right?
>
> So one skilled in the art would understand that the at least ten target loci would be amplified by target specific primers that would avoid the formation of primer dimers, right?
>
> * * *
>
> ***So again, one skilled in the art would understand that in doing this nested PCR, one would design those primers as instructed by the written description using a tool such as Primer3, which is what the patent teaches us to use, and to do that in a way to avoid the formation of primer dimers***.

See, e.g., Ex. L at 150:4-13; 150:25-151:5. When shown this testimony, Dr. Spellman agreed wholeheartedly. *See* Ex. B at 208:18-210:3. If one could avoid the primer dimers that prevent successful multiplex PCR without selecting primers specifically to avoid such primer dimers, Natera's experts never would have said that skilled artisans would "understand" this is how the claims should be practiced.

Natera's inventors agree with Drs. Spellman and Quackenbush. When asked how big of a multiplex PCR one could do without selecting loci to avoid primer dimers, Dr. Zimmerman, for instance, said he would "never run experiments without taking additional measures or measures to avoid primer dimers." Ex. E at 229:8-24; *see also id.* at 76:15-77:8; Ex. F at 166:23-167:11, 232:15-233:11; Ex. H at 145:15-146:4; Ex. G at 65:14-66:21. Such testimony confirms yet again

that skilled artisans could not practice the alleged inventions without undue experimentation absent the very thing that Natera convinced the Court is not part of the claims: selection of primers/loci to avoid unwanted side products. This proves lack of enablement under *Liebel-Flarsheim*.

Notably, Natera's expert opines that the "claimed inventions" are not obvious because the patents state that the inventors made "the surprising discovery that often only a relatively small number of primers in a library of primers are responsible for a substantial amount of the amplified primer dimers that form during multiple PCR reactions." Ex. A ¶¶ 205-206. This is the very disclosure that Defendants cited during claim construction to contend that the claims should require such techniques. *See* D.I. 177 at 13-14. At Natera's urging, the Court rejected this. Natera cannot now credibly rely upon primer selection techniques as an indicator of non-obviousness while at the same time contending that this is unimportant for practicing the invention without undue experimentation.

G. The Priority Applications And Specifications Do Not Adequately Describe The Asserted Claims Of The '220, '482, '172, And '814 Patents

Natera contends that the '220, '482, '172, and '814 patents are entitled to claim the benefit of an October 2011 patent application ("the '508 application") or, alternatively, a November 2011 application ("the '235 application"). As documented below, however, neither these applications nor the patents themselves contain an adequate written description of the asserted claims. Summary judgment of lack of priority and lack of written description is thus warranted.

1. The Inventors Were In Possession Solely Of Techniques That Relied Upon Primer Design

The written description requirement is satisfied only where "the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). The purpose of the written description

requirement "is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345 (Fed. Cir. 2000).

Natera informed the Court during claim construction that it had supposedly invented a new way of solving the primer dimer problem in multiplex PCR ***without*** primer selection techniques. *See* D.I. 185 at 34:9-18. Natera could not have been clearer that its claims thus include no requirements regarding primer selection. *See id.* at 6:3-10, 6:19-7:2, 12:12-22. The Court adopted this interpretation. Yet, to the extent Natera ever possessed a way of doing large scale multiplex PCR, it was solely through the use of techniques that involved primer selection, a point the specifications confirm.

The evidence cited above for enablement shows this. *See supra* Part IV.F. Natera's priority documents and patents are clear that to perform the claimed large-scale multiplex PCR, it is "essential" to identify and eliminate primers that cause primer dimers. *See* Ex. GG at 111:13-16; Ex. HH ¶ 293. The patents explain that the ability to identify and remove these primers is a "surprising discovery." D.I. 391-2, Ex. 5 at 46:34-48. This alleged "surprising discovery" is so critical to the alleged inventions that Natera's own expert even relies upon it as an indicator of non-obviousness. Ex. A ¶¶ 205-206. Contrary to Natera's assertion during claim construction that it had achieved a way of performing large scale multiplex PCR without primer selection techniques, Natera's experts testified that this is not actually possible absent the types of primer selection techniques that Natera characterized in its patents as inventive and "surprising." *See supra* Part IV.F. Nowhere does the specification teach how to perform large scale multiplex PCR without such techniques. To the contrary, it is undisputed that every single one of the 28 working examples in the patents rely upon such techniques. *See* D.I. 419-10 ¶¶ 834-36; Ex. B at 194:9-

16, 197:15-199:4. As Natera's expert, Dr. Quackenbush made clear, one "would understand that in doing this nested PCR, one would design those primers as instructed by the written description using a tool such as Primer3, which is what the patent teaches us to use, and to do that in a way to avoid the formation of primer dimers." Ex. L at 150:25-151:5.

Per the Court's construction, however, Natera's claims do not involve or require such techniques. Natera has thus undisputedly drafted claims far broader than what its specifications support. The Federal Circuit has repeatedly made clear that this leads to a failure of the written description requirement. *See, e.g.*, *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005) ("After reading the patent, a person of skill in the art would not understand how to make a seamless DWT generically and would not understand LizardTech to have invented a method for making a seamless DWT, except by 'maintaining updating sums of DWT coefficients.'"); *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1378-79 (Fed. Cir. 2009) (affirming summary judgment of invalidity to claims covering "spikeless" valves where specification described only valves with spikes); *Rivera v. Int'l Trade Commission*, 857 F.3d 1315, 1321-22 (Fed. Cir. 2017) (affirming invalidity of claims lacking a "pod" requirement where specification supported only embodiments with "pods" and expert testified that embodiments in patent would not work without "pods").

2. Natera's Priority Applications And Patents Do Not Describe Their Alleged Inventions As An Integrated Whole

Natera cannot contend that it invented the idea of nested PCR that appears in the claims of the '220, '482, '172, and '814 patents. This was undisputedly in the prior art. *See supra* Part III.B. To the extent there is anything whatsoever inventive in the claims, the only possible thing it could be is the very particular combinations of recited claim elements. Natera's expert agreed:

> Q. If you – it's the combination of steps in Claim 1 of the '220 patent that you think is novel and inventive. There is not one particular step you'd point

> to and say, this is the one step that makes it novel and inventive. It's the combination of steps; is that – is that fair?
>
> A. In my opinion, it is the nonobvious combination of multiple steps that makes this inventive.

Ex. B at 135:13-23; *see also id.* at 156:24-157:1 ("As I've testified, the inventiveness of the patent is the nonobvious combination of all of the elements.").

Yet, Natera's 200-column specifications, which were drafted nearly a decade ago, never describe the particular combinations of claim elements as an integrated whole. Natera thus cobbled together the claims of the '220, '482, '172, and '814 patents from disparate elements scattered across its kitchen-sink style disclosures. Indeed, Natera's Executive Chairman and named inventor, Matthew Rabinowitz, testified that [redacted] Ex. CC at 331:21-332:14, 392:2-9, 441:6-13. This is thus the classic case where a party sought to capture subject matter it never truly invented through aggressive prosecution of old patent applications when it suddenly became commercially beneficial. This, however, is precisely the type of gamesmanship the written description requirement guards against. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1330 (Fed. Cir. 2003) ("The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not….").

The written description requirement guards against this by, among other things, imposing the rule that a "description that merely renders the invention obvious does not satisfy the requirement." *Ariad Pharms., 598 F.3d at 1352*. In particular, the written description requirement is not met when "the specification provides at best disparate disclosures that an artisan might have been able to combine in order to make the claimed invention." *Flash-Control, LLC*

v. Intel Corp., No. 2020-2141, 2021 WL 2944592, at *4 (Fed. Cir. July 14, 2021). "Instead, the specification must present each claim as an 'integrated whole.'" *Id.* at *3.

Courts have repeatedly made clear that when "evaluating whether the written description requirement has been satisfied, a court does not simply look to see whether the specification contains descriptions of the individual elements of the claim. Rather, a court must look to see whether there is a written description for the entirety of the claimed invention—i.e., the combination of elements." *Trans Video Elecs., Ltd. v. Sony Elecs., Inc.*, 822 F.Supp.2d 1020, 1027 (N.D. Cal. 2011); *see also Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013) ("While the 2000 application provides formal textual support for each individual limitation recited in the claims of the '23 patent, it nowhere describes the actual functioning, thermostable alpha-amylase variants that those limitations together define."); *Purdue Pharma L.P. v. Recro Tech., LLC*, 694 F.App'x 794, 797 (Fed. Cir. 2017) ("To the extent that Purdue contends that a person of skill in the art would isolate and combine aspects from various embodiments in the specifications (including patents incorporated by reference involving a different drug) to obtain the claimed invention, Purdue relies upon the wrong test."); *Hyatt v. Dudas*, 492 F.3d 1365, 1371 (Fed. Cir. 2007) (upholding examiner's rejection where examiner found failure of written description requirement because "while each element may be individually described in the specification, the deficiency was the lack of adequate description of their combination.").

A search through Natera's priority documents and the patents themselves reveals no disclosure corresponding to the claimed invention as an integrated whole, as confirmed by Natera's expert. Beginning with the '508 application (Natera's October 2011 priority document) Dr. Spellman confirmed that there was no such disclosure:

> Q. Okay. Is there – is there any example or description of an embodiment that lays out a process that includes all the steps as laid out in Claim 1 of the '220 patent in – in one discrete package?
>
> A. I – I don't recall that there is.

Ex. B at 182:23-183:4. Summary judgment that the ’220, ’482, ’172, and ’814 patents are not entitled to claim the benefit of the ’508 application is thus warranted.[5]

As to the ’235 application, Natera’s November 2011 priority application, Dr. Spellman identified a single allegedly supporting paragraph:

> Q. Okay. Is there any example or description of an embodiment that lays out a process that includes all the steps as laid out in Claim 1 of the ’220 patent in one discrete package?
>
> A. On page – on page 59 – well, it’s page 35 of the patent, I guess. I don’t know. It’s page 59 of the PDF:
>
> “It is possible to amplify a DNA sample (dilution, purified or otherwise) produced by an STA reaction using tag-specific primers and universal amplification, i.e. to amplify many or all pre-amplified and tagged targets. Primers may contain additional functional sequences, e.g. barcodes, or a full adaptor sequence necessary for sequencing on a high throughput sequencing platform.” That is the claims of the '220 series.

Id. at 185:22-186:13. Dr. Spellman testified that this was the “clearest” disclosure supporting the claim that he could recall in the ’235 application. *Id.* at 189:22-190:4.

This disclosure, however, makes no mention of several claim elements, and thus falls far short of supporting the claims. It does not disclose nested PCR, a first PCR with universal primers, a minimum number of targets, ligation of adaptors, or the specific “molecular barcode” recited in the claims. It also does not disclose the 5,000 target limit recited in claims 6 and 7 of Natera’s ’220 patent. When asked whether the paragraph he identified disclosed ligation of molecular barcodes, Dr. Spellman explained the disclosure was “very, very fuzzy” and lamented

[5] Although Dr. Spellman’s testimony focused on the ’220 patent, given the similarity among the claims of the ’220, ’482, ’172, and ’814 patents, it applies equally to all four patents.

the "imprecise" language. *Id.* at 189:16-21 ("So it's the primer piece that – that's fuzzy here. **Q.** Okay. It's the barcode that's part of the primer; right? **A.** But it says the primer can be a full adapter sequence. It's – it's very, very fuzzy."); *id.* at 189:9-10 ("The – the way molecular biologists speak, as you know, is imprecise.").

As to the patents themselves, when Dr. Spellman was similarly asked to identify any disclosure of all the claim steps in a single discrete package, he pointed to the exact same thing he identified in the '235 application and stated that this was the only such relevant disclosure. *See id.* at 190:6-191:3. Thus, the disclosure of the patents themselves are no better than the deficient and "fuzzy" disclosure in Natera's priority applications, such that the claims are not just unable to claim the benefit of the '235 application, but also invalid for lack of written description.

An inability to identify adequate supporting disclosure in the patents is not unique to Natera's experts. During discovery, Natera had every opportunity to identify such disclosure in response to Defendants' Interrogatory No. 24, which requested identification of "any single embodiment in the specification that…discloses each element of the claim as arranged in the claim." *See* Ex. T at 34. Far from identifying any meaningful disclosure, Natera responded with a wall of citations that encompassed virtually every figure and sentence in its 200 column specifications. *See id.* at 36-37. Even when faced with a motion to compel a more specific response, Natera successfully refused to provide further information. *See* D.I. 363 at 1-2. In this regard, Natera tacitly admits that there is no good disclosure that truly supports the claims as an integrated whole, and that it is instead seeking to take the legally erroneous approach of satisfying the written description through disparate disclosures of individual claim elements scattered across the entirety of the patent. Natera should be held to this, and summary judgment should be granted.

It is unsurprising that both Natera and its experts are unable to identify disclosure that supports the claims as an integrated whole. As documented above, Natera claims it made the inventions of the '220, '482, '172, and '814 patents in the 2011 timeframe. But it never bothered to draft the claims for its alleged invention until nearly a decade later.

Where, as here, a party seeks to use *post hoc* amended claims to capture subject matter it did not invent, summary judgment is warranted. *See, e.g.*, *ICU Medical*, 558 F.3d at 1376-79 (affirming summary judgment for lack of written description where 11 years after original filing patentee amended claims to cover "spikeless" medical valves but left specification describing only "spiked" valves unchanged); *Driessen v. Sony Music Ent.*, 640 F.App'x 892, 896 (Fed. Cir. 2016) (affirming summary judgment of lack of written description, explaining that "[w]hen, as here, a patent applicant adds new claims after the original filing date, 'the new claims…must find support in the original specification.'").

V. ARGUMENTS IN SUPPORT OF EXCLUSION OF TESTIMONY

A. Dr. Spellman's Opinions Regarding Faham Should Be Excluded

In his report, Defendants' expert, Dr. Gregory Cooper, presented detailed opinions with copious record citations establishing that certain claims are invalid in view of the Faham prior art reference. *See, e.g.*, D.I. 419-10 ¶¶ 424-459. Natera's expert's rebuttal encompassed just two pages. *See* Ex. A ¶¶ 157-160. These two pages included nothing more than (1) a table devoid of explanation or analysis that simply identified claim elements allegedly not taught in the prior art, and (2) a single-sentence stating that there would be neither motivation to combine nor reasonable expectation of success due to concerns about "uneven" amplification. *Id.* ¶ 160. As to the latter point, Dr. Spellman admitted at deposition that none of the claims require even amplification. *See* Ex. B at 169:17-20. So, Dr. Spellman's opinion about "uneven" amplification is not just conclusory, but irrelevant.

Dr. Spellman's conclusory and irrelevant opinions on Faham that lack any meaningful analysis are unreliable and unhelpful to the jury and should be excluded under Rule 702. *See, e.g.*, *Magnetar Techs. Corp. v. Six Flags Theme Parks Inc.*, C.A. No. 07-127-LPS-MPT, 2014 WL 529983, at *4 (D. Del. Feb. 7, 2014) (A "court may exclude an expert's testimony or opinion if it is conclusory, lacks analysis, or the chasm between the analysis and opinion cannot be bridged."); *Genband US LLC v. Metaswitch Networks Corp.*, No. 2:14-CV-33-JRG-RSP, 2016 WL 3475688, at *2 (E.D. Tex. Jan. 7, 2016) ("Conclusory opinions unsupported by 'facts or data' and based on no discernable 'principles and methods' are not admissible under Fed. R. Evid. 702."); *Genband US LLC v. Metaswitch Networks Corp.*, No. 2:14-CV-33-JRG-RSP, 2016 WL 98745, at *4 (E.D. Tex. Jan. 8, 2016) ("However, Mr. Lanning's opinions on diligent reduction to practice are wholly conclusory and are therefore not admissible."); *Sprint Commc'ns Co. L.P. v. Vonage Holdings Corp.*, No. 05-2433-JWL, 2007 WL 2572417, at *2 (D. Kan. Sept. 4, 2007) ("Presenting a summary of a proffered expert's testimony in the form of a conclusory statement devoid of factual or analytical support is insufficient to lay the proper foundation for the admission of that testimony."); *Elder v. Tanner*, 205 F.R.D. 190, 193–194 (E.D. Tex. 2001) (excluding patent experts' conclusory opinions regarding infringement, anticipation, and obviousness which contained no discussion of their thought processes because their testimony would not assist the trier of fact in determining the case).

B. Drs. Spellman's and Quackenbush's Opinions On Which Patents Signatera Practices Should Be Excluded

1. Dr. Spellman Has No Basis To Opine On Signatera

Dr. Spellman opines that Natera's Signatera product practices claims 1, 9, and 19 of the '708 patent. Ex. A ¶¶ 194-200. Dr. Spellman, however, failed to reliably assess whether Signatera practices each limitation of the claims, most importantly the requirement that the "the

annealing temperature for the reaction condition is greater than a melting temperature of the at least 2 primers."

For this element, Dr. Spellman relies upon a single Natera document stating that [redacted] *See id.* ¶ 196. Thus, the desired melting temperature range includes a segment that is in [redacted]. Dr. Spellman, however, never looked at even a single actual primer or melting temperature in Signatera to confirm [redacted]. *See* Ex. B at 37:11-15, 38:18-39:3. What's more, pursuant to the Court's construction, all the primers (not just some) must have melting temperatures less than the annealing temperature. *See supra* Part IV.B.1. Dr. Spellman fell far short of showing that any primers, let alone all of them, satisfy the claims.

Additionally, Dr. Spellman had no idea how the Signatera primer melting temperatures are calculated for the purpose of assessing [redacted]. *See* Ex. B at 39:24-40:9. This is critical because the claims require the use of a particular technique to determine melting temperature; Natera contends this must be either Primer3 with SantaLucia parameters or UV light experimental measurement. *See supra* Part IV.E.2. Without knowing what the primers are or how their melting temperatures are calculated, Dr. Spellman cannot possibly accurately opine that Signatera's primers satisfy the claims.

For these reasons, Dr. Spellman's opinions are unreliable and should be excluded.

2. Dr. Quackenbush Has No Basis To Provide An Opinion On Signatera

Dr. Quackenbush opines that Signatera practices not just the '708 patent, but several other Natera patents. Ex. M ¶ 573. Yet, he did no analysis and conducted no claim mapping whatsoever—he even failed to specify which claims Signatera allegedly practices. *Id.* In

deposition, Dr. Quackenbush admitted that he did not analyze the patents and claims to determine if Signatera actually practices them. Ex. L at 80:5-81:21, 82:1-5, 87:21-88:4, 88:12-15, 89:1-5, 96:11-13, 97:1-9. Dr. Quackenbush's statements about patents that Signatera practices are thus based on no facts or analysis and should be stricken.

C. Dr. Spellman's And Mr. Stoll's Opinions On Inventorship Should be Excluded

Natera's experts, Dr. Spellman and Mr. Stoll, opine on inventorship of the '814, '172, '482, and '220 patents. Their methodology, however, consists of nothing more than citing to inventorship oaths submitted to the Patent Office and then asserting that the oaths must be correct because, after all, they were submitted to the Patent Office. *See* Ex. A¶¶ 338-47; Ex. II ¶¶ 146-56. Neither expert performed any analysis of information regarding what the inventors actually worked on and whether this might have reflected a material contribution to the alleged inventions. In fact, during deposition, Dr. Spellman, Natera's technical expert, admitted that he is actually only "relying on Natera to – and the patent office and the patent counsel to identify inventors." Ex. Bat 244:12-14. When further questioned, Dr. Spellman admitted that he did not review any material that may allow him to determine each inventor's contribution:

> I have not been asked to look at the laboratory notebooks and determine who did what, when, and what the invent – inventions were and were not.

Id. at 245:25-246:2; *see also id.* at 242:6-246:14. Natera's ***technical*** expert should not be permitted to testify on inventorship based on Patent Office oaths that he knows nothing about.

Mr. Stoll, a partner at Faegre Drinker Biddle & Reath and Natera's patent law expert, rendered similarly flimsy opinions. His opinions were based solely on whether "the individuals who have been added as inventors…are claiming themselves to be inventors, while none of the individuals who have been removed as inventors appear to be complaining about being removed as such." Ex. II ¶ 151. Mr. Stoll admitted that he has no expertise in the technology of the

patents-in-suit. *See* Ex. JJ at 24:13-16, 101:20-23, 102:7-14. He would thus have no basis to attempt a proper analysis of whether any particular individual engaged in technical work that could constitute an inventive contribution to the patents.

Both experts' opinions should be excluded.

D. Mr. Wojczik's Safe Harbor Opinion Should Be Excluded

It is not "an act of [patent] infringement to…use…or import into the United States a patented invention…solely for uses reasonably related to the development and submission of information under a Federal law which regulates the…use of drugs." 35 U.S.C. § 271(e)(1). The Supreme Court rejected a narrow reading of the Safe Harbor's "reasonably related" provision and instead concluded that "[p]roperly construed," it "leaves adequate space for experimentation and failure on the road to regulatory approval." *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 207 (2005). The "statute "***provides a wide berth***" for the use of patented inventions in activities related to the federal regulatory process. *Id.* at 202. "There is simply no room in the statute for excluding certain information from exemption on the basis of the phase of research in which it is developed or the particular submission in which it could be included." *Id.*

Natera's FDA Safe Harbor expert, Jerzy Wojcik, opines that the safe harbor does not cover certain uses of Defendants' products. As documented below, these opinions are wholesale devoid of reliability and should be excluded.

1. Mr. Wojcik Has No Basis To Render Safe Harbor Opinions

Throughout his report, Mr. Wojcik asserted that certain uses of Defendants' products are not covered by the Safe Harbor. *See, e.g.*, Ex. U ¶¶ 82, 92-97 (uses reasonably related to submissions that are not 510k, PMA, or de novo); ¶¶ 70-79, 83-91, 92-97, 103-107, 108-113 (preclinical studies that have not yet resulted in a final FDA submission); ¶¶ 70-79, 114 (retrospective and reproducibility studies); ¶¶ 52-57, 68-79 (R&D uses undertaken prior to the

creation of a design history file); ¶ 53 (all uses where there is no documented compliance with good laboratory practices regulation).

Mr. Wojcik, however, admitted that he has no basis to opine on this issue. Mr. Wojcik testified that he is not actually an expert in the Safe Harbor. For the question of whether a use relied upon the safe harbor, Dr. Wojcik testified that he actually relied upon the conclusions of Natera's attorneys at McDermott: "the opinion on whether or not those [device uses] are or are not within Safe Harbor, I rely on the McDermott organization or other expert witnesses familiar with law." Ex. V at 48:18-24. In this regard, it appears that Mr. Wojcik was not acting as an independent expert, but merely a mouthpiece to regurgitate Natera's attorneys' positions.

Indeed, Mr. Wojcik testified that his only knowledge of the Safe Harbor came from instruction by counsel and by doing "a Google search." *Id.* at 42:9-20. He also testified that prior to his engagement in this case, he had no experience whatsoever with the Safe Harbor. *Id.* Prior to the deposition, Mr. Wojcik had never even read the Safe Harbor statute. *Id.* at 51:4-6. On these grounds alone, Mr. Wojcik's opinions should be stricken. *See Willis v. Besam Auto. Entrance Sys., Inc.,* No. 04-CV-0913, at *14 (E.D. Pa. Nov. 3, 2005) (precluding testimony from expert with "no specialized knowledge or experience" as it is "nothing more than a subjective belief").

2. Mr. Wojcik's Ignorance Of Safe Harbor Renders Opinions Unreliable

In light of Mr. Wojcik's ignorance of the Safe Harbor, it should come as no surprise that many of his opinions are incorrect as a matter of law. As documented below, the limited understanding of the safe harbor that Dr. Wojcik seemingly gleaned from Natera's outside counsel was exceedingly narrow and contrary to law. This erroneous understanding of the Safe Harbor infected his opinions, rendering them erroneous and unreliable.

a. Mr. Wojcik's Erroneously Narrow Safe Harbor Understanding

Examples demonstrating Mr. Wojcik's failure to understand the Safe Harbor are legion.

First, Mr. Wojcik testified that the Safe Harbor is limited to development of information for inclusion in an FDA submission. Ex. V at 87:15-20. The Supreme Court in *Merck*, however, was clear that "Congress did not limit § 271(e)(1)'s safe harbor to the development of information for inclusion in a submission to the FDA….Rather, it exempted from infringement all uses …'reasonably related' to the process of developing information for submission." *Merck*, 545 U.S. at 206. To conclude otherwise, the Supreme Court held, fails to "protect research." *Id.*

Second, Mr. Wojcik testified that preclinical studies that fail to result in a final FDA submission are not covered by the Safe Harbor. Ex. V at 91:21-93:18. In *Merck*, however, the Supreme Court explicitly concluded that such uses are covered. *Merck*, 545 U.S. at 208; *see id.* at 202 (providing that the Safe Harbor "necessarily includes preclinical studies"). In the same vein, Mr. Wojcik testified that the Safe Harbor only applies where there is an intent to proceed to a ***final*** FDA submission. Ex. V at 75:8-76:4. Neither the statute nor case law imposes this onerous, ends-based requirement. *Merck*, 545 U.S. at 206.

Third, Mr. Wojcik repeatedly asserted that for the Safe Harbor to apply, the use must be conducted in conformity with the FDA's good laboratory practices regulations. Ex. V at 62:16-71:15. Again, the Supreme Court expressly rejected this argument on multiple grounds. *Merck*, 545 U.S. at 204. Mr. Wojcik also testified that for a use to fall under the Safe Harbor, it had to adhere to the § 820.30 of the Code of Federal Regulations regarding design controls. Ex. V at 57:24-58:24; 71:17-72:21; 94:3-105:23; 108:17-111:11; 111:15-25; 116:5-10. There is, however, no such requirement in the statute or on the case law.

Fourth, Mr. Wojcik testified that the Safe Harbor only applies to 510k, PMA, or de novo

submissions to the FDA. *Id*. at 76:24-77:8. And he testified that the Safe Harbor does not apply to uses supporting a "Q submission," a presubmission seeking FDA feedback. *Id.* at 87:4-13; 209:4-8; *see* Ex. W ¶ 58. The Supreme Court, however, determined in *Merck* that the Safe Harbor "extends to all uses of patented inventions that are reasonably related to the development and submission of ***any*** information under the FDCA." *Merck*, 545 U.S. at 202; *see also Edwards Lifesciences Corp. v. Meril Life Sciences Pvt. Ltd.*, No. 19-cv-06593-HSG, 2020 WL 6118533, at *10 (N.D. Cal. Oct. 16, 2020) (concluding that uses relating to the mere preparation of a draft presubmission—which had not yet been submitted to the FDA—falls under the Safe Harbor).

Fifth, Mr. Wojcik testified that the Safe Harbor does not apply to uses that occur in the research and development stage. Ex. V at 87:22-88:8; 91:3-10; Ex. U ¶ 47. The Supreme Court, however, has held that "[t]here is simply no room in the statute for excluding certain information from the exemption ***on the basis of the phase of research in which it is developed.***" *Merck*, 545 U.S. at 202. Mr. Wojcik stated that nearly 90% of a product's development occurs in R&D. Ex. U ¶ 47. Therefore, according to Mr. Wojcik's understanding of the Safe Harbor, 90% of a product's development would fall outside the Safe Harbor. This is contrary to law. *Merck, 545 U.S.* at 206 (construing the Safe Harbor "***to protect research***").

As the foregoing establishes, Mr. Wojcik's opinions started from a fundamentally flawed foundation and should be excluded for this reason alone.

b. Mr Wojcik's Flawed Understanding Led To Erroneous Opinions

While the examples above illustrating Mr. Wojcik's total misunderstanding of the Safe Harbor fully justify exclusion on their own, the extent to which this misunderstanding infected Mr. Wojcik's opinions further establishes that his opinions should be excluded. Mr. Wojcik erroneously excludes several types of product use that, on their face, are undeniably protected by

the Safe Harbor:

- Uses reasonably related to submissions that are not 510k, PMA, or de novo, such as the STRATAFIDE presubmission and PCM and STRATAFIDE Breakthrough Device Designations. Ex. U ¶¶ 82, 92-97. The Safe Harbor covers uses reasonably related to ***any*** FDA submission. *Merck*, 545 U.S. at 202.

- Preclinical studies that have not yet resulted in a final FDA submission, including all [redacted] Ex. U ¶¶ 70-79, 83-91, 92-97, 103-107, 108-113. The Supreme Court expressly held the Safe Harbor "necessarily includes preclinical studies." *Merck*, 545 U.S. at 202.

- All retrospective and reproducibility studies reasonably related to an FDA submission. Ex. U ¶¶ 70-79, 114. The Safe Harbor covers all uses that are "reasonably related" to an FDA submission, even if that use data is not directly submitted to the FDA. *Merck*, 545 U.S. at 206.

- R&D uses undertaken prior to the creation of a design history file. Ex. U ¶¶ 52-57; 68-79. This is not so, as the Supreme Court recognized that the Safe Harbor is designed "to protect research." *Merck*, 545 U.S. at 206.

- All uses where there is no documented compliance with the good laboratory practices regulation. Ex. U ¶ 53. The Supreme Court expressly rejected this. *Merck*, 545 U.S. at 204.

As the foregoing shows, Dr. Wojcik's misunderstanding of the safe harbor was not inconsequential or harmless, but rather led him to make facially incorrect conclusions about what falls within the safe harbor. This further supports exclusion of his testimony. *See Chemipal Ltd. v. Slim-Fast Nutritional Foods Intn'l., Inc.*, 350 F.Supp.2d 582, 592, 594 (D. Del. 2004) (precluding expert opinion where the "lack of familiarity with the methods and the reasons underlying" them failed to "bridge the 'analytical gap between the data and the opinion offered'" and "virtually precluded any assessment of the validity of the [opinion] through cross examination").

3. Mr. Wojcik's Opinions Are Unreliable Because They Are Based On Misunderstanding And/Or Mischaracterization Of Evidence

Mr. Wojcik's opinions should also be excluded because they are based on a misunderstanding and/or mischaracterization of the factual evidence. Mr. Wojcik's opinions are

replete with examples.

As one example, Mr. Wojcik testified that [redacted], citing for support the testimony of Defendants' Vice President of Global Regulatory Affairs, Timothy Holwick. Ex. U ¶ 89 (citing Ex. X); *see* Ex. V at 77:9-78:1 (same). Mr. Holwick, however, said no such thing. Ex. X at 202:11-18. When confronted with Mr. Holwick's transcript, Mr. Wojcik agreed that the testimony did not support his statement, but refused to clarify his report. He asserted that the assays being run were not related to the PCM product. Ex. V at 75:25-76:10. This too is incorrect, as Mr. Wojcik later admitted. *Id*. at 146: 20-25; 151:1-13; 162:8-18.

Mr. Wojcik also cited Mr. Holwick's testimony as allegedly establishing that "the PCM assays run as part of the Phase II process will not be submitted to the FDA." Ex. U ¶ 89 (citing Ex. X at 212:5-20). Mr. Holwick actually said the exact opposite, to which Mr. Wojcik admitted. Ex. X at 212:5-20; *see* Ex. V at 82:14-22. Mr. Wojcik also argued that Defendants had no intention to submit a PCM IVD filing, again relying upon Mr. Holwick's deposition for this proposition. Ex. U ¶ 76 (citing Ex. X at 79:14-15). [redacted] Ex. X at 79:14-23.

As yet another example, Mr. Wojcik opined that Defendants' witness Dr. Daber testified that certain studies "are RUO projects." Ex. U ¶ 74 (citing Ex. Y at 119:11-17). Upon reviewing Dr. Daber's testimony, however, Mr. Wojcik agreed that the FDA submission referenced in his citation was related to a PCM FDA submission and would thus be covered by the safe harbor. Ex. V at 186:8-188:7.

Mr. Wojcik's repeated mischaracterization of evidence to support his opinions further establishes that they are unreliable and should be excluded.

E. Dr. Sullivan's Opinions Regarding The BD-ArcherDX Agreement Should Be Excluded

Archer pays a [redacted] under a license with Becton-Dickinson ("the BD-ArcherDX agreement") for rights to patents covering "molecular barcodes" for increasing sensitivity of mutation detection.[6] Ex. Z at 75:6-76:19; Ex. AA ¶ 395. Natera's technical expert, Dr. Quackenbush, asserts that the patents in this agreement "have limited comparability with the Asserted Patents." Ex. M ¶ 582. Nevertheless, Natera's damages expert, Dr. Sullivan, uses the BD-ArcherDx agreement as his principal comparable license for his proposed royalty rate for the Asserted Patents. To do so, he "adjusts" the paid [redacted] in the BD-ArcherDX agreement by nearly a factor of [redacted] 19.7%. Ex. AA ¶ 404.

This "adjustment" is no such thing. It is a fundamentally unsound royalty rate that is at best based upon a non-comparable license and at worst drawn from whole cloth that fails to apportion damages to the incremental benefit (if any) from the Asserted Patents. "The essential requirement is that the ultimate reasonable royalty award must be based on the ***incremental*** value that the patented invention adds to the end product." *Ericsson, Inc. v. D-Link Sys., Inc.*, 773 F.3d 1201, 1226 (Fed. Cir. 2014). "When a patent covers the infringing product as a whole, and the claims recite both conventional elements and unconventional elements, the court must determine how to account for the relative value of the patentee's invention in comparison to the value of the conventional elements recited in the claim, standing alone." *AstraZeneca AB v. Apotex Corp.*, 782 F.3d 1324, 1338 (Fed. Cir. 2015); *see also Omega Pats., LLC v. CalAmp Corp.*, 13 F.4th 1361, 1380 (Fed. Cir. 2021). Dr. Sullivan's opinions fails these standards because it improperly includes value from prior art and techniques unrelated to the Asserted Patents.

[6] The baseline rate in this agreement is [redacted] but due to various adjustments the actual paid royalty rate is only [redacted].

1. Dr. Sullivan Fails To Apportion For The Incremental Benefit Over The Use Of Molecular Barcodes

It is undisputed that the use of molecular barcodes for variant detection is in the prior art and is used by the Accused Products. Ex. B at 88:23-90:1; Ex. C at 106:16-25. Dr. Sullivan, however, attributes the benefits of molecular barcodes to the Asserted Patents, failing to exclude the benefits of prior art technology that Defendants had long since licensed. In essence, Dr. Sullivan's proposed royalty is based on the illogical and flawed proposition that Defendants would agree to pay twice for the same technology (*i.e.*, molecular barcodes).

Dr. Sullivan's flawed methodology is reflected in Attachment J-4 to his report. Ex. AA at Attachment J-4. First, he compares a method ***without*** molecular barcodes to one ***with*** molecular barcodes, and asserts that the latter works 95% better. *Id.* at line [D]. Second, Dr. Sullivan alleges that there is an additional 92% improvement on going from the method ***with*** molecular barcodes to Defendants' accused personalized cancer monitoring product. *Id.* at line [E]. Given that molecular barcodes are undisputedly a prior art technique, one might logically expect Dr. Sullivan to contend that the royalty rate for the Asserted Patents should at most reflect the economic value of the 92% improvement that arises from things ***other*** than molecular barcodes.

Dr. Sullivan, however, proceeds to ***combine*** the 95% improvement from molecular barcodes with the 92% improvement afforded by Defendants' accused technology to yield an overall improvement of 187%. *Id.* at line [F]. Pointing to the base (but not actually paid) royalty of [redacted] in the BD-ArcherDX agreement, Dr. Sullivan arrives at an overall royalty rate of 19.7% for the Asserted Patents. This encompasses [redacted] for molecular barcodes plus an additional [redacted] to reflect the additional 92% improvement afforded by Defendants' personalized cancer monitoring technology. This is nearly double the base [redacted] rate in the BD-ArcherDX agreement, which itself is [redacted] Defendants actually pay once

adjustments are taken into account. Ex. AA at ¶ 404. The key point, however, is that Dr. Sullivan fails to exclude from his proposed royalty the benefits provided by prior art molecular barcoding techniques. Failing to reflect proper apportionment, Dr. Sullivan's opinions should be excluded.

2. Dr. Sullivan Fails To Apportion For The Incremental Benefit Over The Use Of Personalization

Dr. Sullivan's "adjustment" of the royalty rate in the BD-ArcherDX agreement also improperly includes benefits from the ***personalization*** of Archer's Accused Product, a feature that is totally unrelated to the Asserted Patents.

One of Archer's products, PCM, is personalized to an individual's tumor so that if cancer returns, it can be more easily detected. Indeed, "PCM" is short for "personalized cancer monitoring" and is the product referred to in Attachment J-4 of Dr. Sullivan's report. Dr. Sullivan discusses at length the unique benefits of personalization. *See, e.g.*, Ex. AA ¶ 242 ("Further, evidence indicates that tumor-informed, personalized assays are differentiated from other ctDNA MRD assays."); *id* at ¶ 244 ("Not only are personalized approaches distinguished from tumor-naïve approaches such as Guardant, but also Natera is distinguished within the personalized marketplace."); Ex. BB at 114:11-115:2.

Nothing in the Asserted Patents, however, relates to personalization, and none of the claims require this. Nevertheless, Dr. Sullivan's 19.7% royalty rate ***includes*** the economic value of personalization. This is again clear from Dr. Sullivan's report. Dr. Sullivan's primary evidence for his [redacted] is a single Archer slide showing the performance for "fixed" (*i.e.*, non-personalized) methods, "personalized" methods, and Archer's personalized cancer product. Ex. AA ¶ 401. The slide shows a five-fold performance increase on going from non-personalized methods to personalized method (even ***without*** Archer's

technology). *Id.* (showing a decrease in the limit of detection from 0.05 for a fixed panel method to 0.01 for a personalized method).

While one would have expected Dr. Sullivan to exclude the economic value of personalization from his royalty rate since personalization has nothing to do with the Asserted Patents, he instead uses the full 92% improvement resulting from Defendant's personalized cancer product, including the portion of improvement from personalization. *See* Ex. AA at Attachment J-4.

Because Dr. Sullivan's royalty rate erroneously reflects not just the incremental value of the Asserted Patents, but also the value of prior art and unclaimed features, it fails to properly apportion and should be excluded.

VI. CONCLUSION

For the foregoing reasons, Defendants' motion should be granted.

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Respectfully submitted,

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